Emtricitabine

Brand Name: Emtriva
Drug Class: Nucleoside Reverse Transcriptase Inhibitors

Drug Description

Emtricitabine, also referred to as FTC, is a nucleoside reverse transcriptase inhibitor (NRTI). Emtricitabine is the (-) enantiomer of a thio analogue of cytidine; it differs from other cytidine analogues by a fluorine in the 5 position. [1]

HIV/AIDS-Related Uses

Emtricitabine was approved by the FDA on July 2, 2003, for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults age 18 and older. Emtricitabine oral solution was approved by the FDA on September 28, 2005 and is approved for use with other anti-HIV drugs for the treatment of HIV-1 infection in patients over 3 months of age. Emtricitabine may be considered for treatment-experienced patients with HIV strains that are susceptible to emtricitabine as assessed by genotypic or phenotypic testing.[2]

Pharmacology

Emtricitabine, a synthetic nucleoside analogue of cytosine, undergoes phosphorylation by cellular enzymes to emtricitabine 5'-triphosphate. The active phosphate drug inhibits viral DNA synthesis by competing with the natural substrate deoxycytidine 5'-triphosphate for incorporation into viral DNA and terminating the DNA chain at the point of incorporation.[3]

Emtricitabine is rapidly and extensively absorbed following oral administration, reaching peak plasma concentrations (Cmax) at 1 to 2 hours post-dose. In one clinical trial, the mean absolute bioavailability of emtricitabine was 93% following multiple doses of the drug. The mean steady state Cmax was 1.8 mcg/ml and the area under the plasma concentration-time curve (AUC) over a 24-hour dosing interval was 10.0 hr-mcg/ml. The mean steady state plasma trough concentration 24 hours after an oral dose was 0.09 mcg/ml.[4]

Emtricitabine is in FDA Pregnancy Category B. Animal studies reveal no increased incidences of fetal variations or malformations in mice and rabbits at 60- and 120-fold higher drug exposures, respectively, than the human exposure at the recommended daily dose. However, there are no adequate and well-controlled studies in pregnant women. Results of animal studies are not always predictive of human response, and emtricitabine should be used during pregnancy only if clearly needed. An Antiretroviral Pregnancy Registry has been established to monitor fetal outcomes when the mother was exposed to antiretroviral drugs during pregnancy. Healthcare providers can register patients at http://www.APRegistry.com or by calling 1-800-258-4263. It is not known whether emtricitabine is distributed into human milk. Mothers should avoid nursing while taking emtricitabine.[5]

Emtricitabine is less than 4% bound to plasma proteins, and protein binding is independent of drug concentration over a range of 0.02 to 200 mcg/ml. In vitro studies indicate that emtricitabine does not inhibit CYP450 enzymes. Biotransformation occurs through glucuronidation and oxidation. Following administration of 14C-emtricitabine, 86% of the dose was recovered in urine and 14% in feces. Of the urine-recovered dose, 13% was recovered as metabolites, including 3'-sulfoxide diastereomers and 2'O-glucuronide. The plasma half-life of emtricitabine is approximately 10 hours. Renal clearance of the drug exceeds estimated creatinine clearance, indicating elimination by both glomerular filtration and active tubular secretion. In patients with renal impairment, both Cmax and AUC were increased.[6] Hemodialysis treatment removes about 30% of an emtricitabine dose over a 3-hour period, but it is unknown whether emtricitabine can be removed by peritoneal dialysis.[7]

HIV isolates with reduced susceptibility to emtricitabine have been recovered from some patients treated with emtricitabine alone or in combination with other antiretroviral agents. Viral isolates from 37.5% of patients with virologic failure had reduced susceptibility to emtricitabine, attributed to M184V/I mutations in the HIV reverse transcriptase gene. Cross resistance has been noted among some nucleoside analogues. Emtricitabine-resistant isolates were cross-resistant

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Pharmacology (cont.)

to lamivudine and zalcitabine, but retained susceptibility to abacavir, didanosine, stavudine, tenofovir, and zidovudine, as well as to the non-nucleoside reverse transcriptase inhibitors delavirdine, efavirenz, and nevirapine. Viruses with mutations leading to decreased susceptibility to stavudine, zidovudine, or didanosine remained sensitive to emtricitabine. Isolates containing the K65R mutation demonstrated decreased susceptibility to emtricitabine.[8]

Adverse Events/Toxicity

The most frequently reported adverse effects of emtricitabine are mild to moderate headache, nausea, diarrhea, and skin rash. Skin discoloration on palms and soles was reported with higher frequency in emtricitabine-treated patients than in controls, but the mechanism of skin discoloration is unknown.[9]

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including emtricitabine. In some patients coinfected with HIV and hepatitis B, exacerbation of hepatitis has been reported after discontinuing treatment with emtricitabine.[10]

Redistribution of body fat, peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been observed in patients receiving antiretroviral therapy.[11]

Treatment-emergent grade 3 or 4 laboratory abnormalities have been reported in at least 1% of patients receiving emtricitabine. These abnormalities include triglycerides greater than 750 mg/dl and creatine kinase over four times the upper limit of normal.[12]

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including emtricitabine. During the initial phase of combination antiretroviral treatment, a patient whose immune system improves may develop an inflammatory response to indolent or residual opportunistic infections, such as Mycobacterium avium infection, cytomegalovirus infections, Pneumocystis jirovecii pneumonia, or tuberculosis. Symptoms of immune reconstitution syndrome necessitate further evaluation and treatment.[13]

Drug and Food Interactions

Emtricitabine capsules and oral solution may be administered with or without food. AUC was unchanged and Cmax decreased by 29% when the capsule form of the drug was administered with a 1,000-calorie, high-fat meal. AUC and Cmax were unaffected when oral solution was administered with either a high- or low-fat meal.[14]

Emtricitabine has been evaluated in healthy volunteers in combination with tenofovir disoproxil fumarate (TDF), zidovudine, indinavir, famciclovir, and stavudine. A 20% increase in plasma trough concentrations of emtricitabine occurred when it was administered concurrently with TDF. When emtricitabine was given concurrently with zidovudine, zidovudine's AUC and Cmax increased by 13% and 17%, respectively.[15] Because renal elimination of emtricitabine is through glomerular filtration and active tubular secretion, there may be competition for elimination with other compounds that are also renally eliminated.[16]

Contraindications

Emtricitabine is contraindicated in patients with previously demonstrated hypersensitivity to any of the components of the drug product. Emtricitabine should be discontinued in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or severe hepatotoxicity. There have been reports of severe acute exacerbations of hepatitis B after discontinuation of emtricitabine treatment in patients coinfected with HIV and HBV; hepatic function should be monitored closely for at least several months after discontinuing emtricitabine in such patients.[17]

Clinical Trials

For information on clinical trials that involve Emtricitabine, visit the ClinicalTrials.gov web site at http://www.clinicaltrials.gov. In the Search box, enter: Emtricitabine AND HIV Infections.

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Dosing Information

Mode of Delivery: Oral.[18]

Dosage Form: Capsules containing emtricitabine 200 mg.[19]

Oral solution containing emtricitabine 10 mg/ml.[20]

The recommended dose of emtricitabine for adults is 200 mg in capsule form or 240 mg (24 ml) oral solution once a day in combination with other antiretroviral agents. The recommended dose of emtricitabine for children is based on age and weight. Children who weigh more than 33 kg (72.8 lbs) and who can swallow an intact capsule should take 200 mg in capsule form once a day in combination with other antiretroviral agents.[21]

The dosing interval of emtricitabine in capsule form should be adjusted in patients with baseline creatinine clearance (CrCl) less than 50 ml/min as follows: 200 mg every 48 hours for CrCl 30 to 49 ml/min; 200 mg every 72 hours for CrCl 15 to 29 ml/min; and 200 mg every 96 hours for CrCl less than 15 ml/min. The dosing interval of emtricitabine oral solution should be adjusted with baseline CrCl less than 50 ml/min as follows: 120 mg (12 ml) every 24 hours for CrCl 30 to 49 ml/min; 80 mg (8 ml) every 24 hours for CrCl 15 to 29 ml/min; and 60 mg (6 ml) every 24 hours for CrCl less than 15 ml/min. There are insufficient data to recommend a specific dose adjustment of emtricitabine in pediatric patients with renal impairment, but a reduction in dose or an increase in the dosing interval similar to adjustments for adults should be considered for these patients. Patients on hemodialysis should also receive emtricitabine 200 mg every 96 hours after completion of dialysis, if on the same day.[22]

Storage: Store capsules at 25 C (77 F); excursions permitted at 15 C to 30 C (59 F to 86 F). Store oral solution refrigerated at 2 C to 8 C (36 F to 46 F); oral solution should be used within 3 months if stored by the patient at 25 C (77 F), with excursions permitted at 15 C to 30 C (59 F to 86 F).[23]

Chemistry

CAS Name: (2R-cis)-4-Amino-5-fluoro-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl] -2(1H)-pyrimidinone[24]

CAS Number: 143491-57-0[25]

Molecular formula: C8-H10-F-N3-O3-S[26]

C38.86%, H4.08%, F7.68%, N17.00%, O19.41%, S12.97%[27]

Molecular weight: 247.25[28]

Melting point: 136 C to 140 C (276.8 F to 284 F) as solid white from ether and methanol.[29]

Physical Description: White to off-white powder.[30]

Solubility: Approximately 112 mg/ml in water at 25 C (77 F).[31]

Other Names

524W91[32]

BW524W91[33]

FTC[34]

Coviracil[35]

Emtricitabina[36]

Further Reading

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Manufacturer Information

Emtricitabine
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For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

• Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET

• Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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